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Banking feces: a new frontier for public blood banks?

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Fecal microbiota transplantation (FMT) is an effective treatment for recurrent *Clostridioides difficile* infection and is potentially beneficial in other microbiota-related disorders. The provision of FMT in routine clinical practice requires an extensive infrastructure that is reliant on voluntary donors. Alongside an increasing demand for FMT, the logistic barriers of a large-scale donor-dependent operation and the difficulties among health authorities to regulate FMT limit the dissemination of sustainable FMT services. Blood centers are large organizations that handle a multitude of donor-dependent operations on a daily basis. Blood and feces share many of the same dependencies, and feces may present a new opportunity for the blood services to handle. In this paper, we describe how an FMT service may be established and embedded within the blood service infrastructure, and we explain the benefits of using blood donors as feces donors. We further explore the current indications of FMT, the challenges related to the lack of legislation, and the future perspectives for blood banks to meet a new and increasing demand.

Fecal microbiota transplantation (FMT) is the transfer of an entire fecal microbial community from a donor to a patient who has a disturbed or depleted intestinal microbial ecosystem.[1] The technique has been known and practiced for centuries. Records of crude FMT treatments date back to the fourth century in China, where the consumption of a mixture of fecal matter and water, referred to as "yellow soup," was used as a means to treat food poisoning and diarrhea.[2,3] In modern medicine, the first successful FMTs were reported in 1958 by Eiseman and coworkers,[4] who treated four patients with pseudomembranous colitis caused by *Clostridioides* (formerly *Clostridium*) *difficile* (CD), which was unknown at that time. Since then, resolution rates of 70% to 90% following FMT for recurrent CD infection (rCDI) have been consistently reported in both observational studies[5–9] and randomized trials.[10–14]

ABBREVIATIONS: CD = *Clostridioides difficile*; EUTCD = European Tissue and Cells Directive; FMT = fecal microbiota transplantation; IND = investigational new drug; rCDI = recurrent *Clostridioides difficile* infection.

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During the past decade, the increased understanding of the human intestinal microbiota and its role in health and disease development have sparked a new interest in the use of FMT. Disturbances of the gut microbiota have been associated with a range of extraintestinal disorders such as obesity, diabetes, and allergies.[15,16] For disorders in which a causal effect of the microbiota can be established, FMT potentially offers a new treatment approach that, contrary to antibiotic treatments, has a restorative intent.

The high success rate of FMT in treating rCDI has prompted intense development of the treatment approach. In recent years, the FMT procedure has undergone drastic improvements, shifting from low-tech applications using kitchen devices and fresh feces obtained from relatives to capsules containing rigorously screened feces from healthy, anonymous donors.[17–19] While FMT procedures have been developed and optimized, the widespread dissemination of FMT to the broader public is limited by logistical barriers and a struggle regarding the regulation of FMT by competent authorities.

A feasible solution to meet these challenges may be a collaboration with national blood centers. Today, blood service organizations are large and complex organizations that handle blood donor recruitment, blood donation, and product processing, testing, and release. They thereby secure the blood components needed for lifesaving transfusions for millions of patients each year. Globally, an estimated 112.5 million transfusions take place each year.[20] The transfusion of safe blood to patients is a necessary component of a modern health care system, and a multitude of other treatments depend on this process. Less than 100 years ago, blood donation and transfusion started out as initiatives driven by pioneering doctors and altruistic volunteers.[21] Similarly, this is where FMT is today, with individual initiatives driven by a few physicians. We point out that both the regulatory framework and the principles of practice used by existing blood service organizations are readily applicable to FMT services.

In the present paper, we report our experiences with establishing an FMT service developed with the blood service infrastructure. We focus on the steps involved in recruiting and screening feces donors to produce ready-to-use fecal suspensions. We describe the challenges related to the lack of legislation and the future perspectives for blood banks to meet a new and increasing demand for fecal transplantation.

INDICATIONS AND MODE OF ACTION FOR FMT

The main indication for FMT is rCDI, refractory to the standard treatment with metronidazole, vancomycin, or fidaxomicin.[22,23] The clinical symptoms of rCDI range from persistent diarrhea to life-threatening pseudomembranous colitis with megacolon. In several clinical trials, FMT has proved superior to antibiotics for the treatment of rCDI with resolution rates ranging from 70% to 90%.[10–14] As a result, European and US clinical guidelines now recommend FMT as a second-line treatment for rCDI.[22,23]

The growing appreciation for FMT as a potential treatment for intestinal microbiota disruption has generated an increased interest in FMT for the treatment of other microbiota-sensitive diseases. Numerous clinical trials are currently investigating FMT for other indications such as inflammatory bowel diseases,[24–26] irritable bowel syndrome,[27–29] hepatic encephalopathy,[30] metabolic syndrome,[31,32] graft-versus-host disease,[33] and multidrug-resistant infections.[34] Despite promising results, the current evidence for the therapeutic effect of FMT on these conditions is weak or contradictory. The long-term effects of FMT are sparsely described, and adverse events are underreported.[35,36]

The mode of action of FMT remains elusive. Most of our knowledge comes from studies of patients with rCDI, where gut physiology normalization and symptom resolution occurs within days of the procedure.[37] FMT drives a variable engraftment of a donor-like bacterial community that, however, does not necessarily determine the treatment response.[38] Well-defined bacterial cocktails may be successfully applied for the treatment of rCDI,[39] but the effect may rely on specific properties, such as bile salt hydrolase activity, shared by groups of bacteria rather than the presence or absence of specific strains.[40] Regarding other diseases such as inflammatory bowel disease, irritable bowel syndrome, hepatic encephalopathy, or graft-versus-host disease, which all have less well-defined underlying etiologies, the composition of the transplanted microbes or the requirements for specific strains may differ from those associated with the treatment of rCDI. The intriguing finding that sterile-filtrated fecal water is effective for rCDI[41] suggests that nonbacterial substances, such as metabolites, host factors, or bacteriophages, contribute to the therapeutic effect.[42] Recent studies identified bacterial metabolites, such as the short-chain fatty acid valerate, as important key factors for understanding the mode of action of FMT.[43] Taken together, the determinants for successful FMT are numerous and are not restricted to the action of live intestinal bacteria. The studies highlight the complexities through which FMT exerts its modes of action.

INFRASTRUCTURE OF AN FMT SERVICE

An FMT service may be divided into three overall components: 1) donor recruitment and screening, 2) laboratory processing, and 3) clinical application. These components greatly resemble the infrastructure needed to collect, process, and provide other donor-dependent products such as blood, plasma, stem cells, and sperm. In the following section, we describe the steps needed to produce a ready-to-use fecal suspension compliant with the European Tissue and Cells Directive (EUTCD).[19,44]

Donor recruitment with baseline characteristics and prescreening

An FMT service greatly depends on access to healthy donors. A sustained effort to recruit donors is necessary and represents two related challenges: accessing enough potential donors and selecting only the healthy donors. We do not know exactly what constitutes a healthy intestinal microbiota. Prior studies that investigated the effects of FMT mostly recruited healthy, normal-weight donors who met several health-related criteria, such as the absence of chronic diseases, allergies, high-risk behavior, depression, family history of malignancy, and use of medication.[10,12,17]

Donor screening

Given the potential implications of transferring pathogenic microorganisms, a cautious approach to screening has been applied in most studies and guidelines.[1,45–48] This is analogous with the procedures employed by blood service organizations and emphasizes the need for voluntary (i.e., unpaid) donations. Since the emergence of the HIV epidemic in the 1980s and the unforeseen transmission of HIV to recipients through blood or plasma-derived products,[49] the precautionary principle has been applied to new and emerging potential threats to blood safety. The precautionary principle aims to ensure that potential risks to blood safety are mitigated by either the deferral of donors (e.g., based on symptoms or travel history) through screening or by pathogen inactivation. While the precautionary principle has helped to reduce the risk of transfusion-transmitted infectious diseases to very low levels in most high-income countries, avoiding unnecessary criteria and testing that reduces the number of eligible donors is also necessary. Because of the very low specificity of several deferral criteria, the cost per quality-adjusted life year gained is high for many of the criteria.[50] For FMT, we still know little about the optimal criteria and screening targets. Consequently, all donors are screened for infections and noninfectious diseases with an extensive panel that includes blood and fecal tests as well as health questionnaires (Table SS1, available as supporting information in the online version of this paper).[1,17,47,51] The risk of false-positive test results is high, and the number of eligible donors is reduced with an increase in screening parameters. Papers that describe the recruitment and screening of FMT donors report overall eligibility rates of 3%, which makes donor recruitment an important limiting factor in FMT operations.[46,52] Eligible feces donors are tested repeatedly, and, as with blood, their donations are quarantined until all postdonation screening results have been approved.

Laboratory processing

Feces donors either produce fecal products at home or at facilities provided by the FMT institution. When kept cooled at 4°C, the fecal microbial community remains stable for up to 8 hours before any detectable changes occur.[53] Accordingly, home donations should preferably be delivered to the FMT institution within 2 hours to ensure microbial viability and quality while giving the time for the processing.[19] Before being applicable for clinical use, the feces must undergo a series of processing steps that preserve the microbiota and render a uniform, ready-to-use fecal suspension. The methods differ according to the intended administration form, but the processing principles are similar; the fecal sample is first diluted in saline, homogenized, and crude-filtered; then cryoprotectant glycerol or branched carbohydrates are added. The fecal suspensions are then dispersed into containers or capsules and stored at −80°C until use. Overall, the processing aims to preserve a fecal microbiota composition similar to that of the crude, unprocessed feces. Although the effects of each handling step on factors such as viability and bacterial composition are unknown, cryopreservation does not affect the clinical efficacy of FMT in patients with rCDI.[54] On the day of clinical application, the frozen suspension is thawed before use. The suspension is linked to the recipient in a database, and the final package is then delivered at the clinical ward for administration.

Clinical application

Fecal microbiota transplantation may be applied to either the upper or the lower gastrointestinal tract. For the upper tract, FMT may be administered by nasojejunal tube insertion, gastroscopy, or acid-resistant capsules. For the lower gastrointestinal tract, FMT may be administered by colonoscopy, sigmoidoscopy, or retention enemas. Colonoscopy is regarded as the gold standard,[55] but the clear benefits of an encapsulated FMT, which can be ingested by the patient without the requirement for bowel lavage or hospitalization, make this the most practical mode of application. As an adjuvant treatment option to FMT, preceding bowel lavage may be used to facilitate the passing of the residual gut microbiota thereby reducing the recipient's microbial load.[56]

Implementing an FMT service in clinical practice is time consuming and requires significant resources. Given these practical implications, stool banks across the United States, Europe, and Asia have been formed to meet the increasing demand for fecal donations.[46] Stool banks recruit and screen donors, process the donations, and deliver a standardized feces suspension ready for clinical use. This offers clinical institutions an easy option to routinely perform FMT.

Traceability and quality control

FMT should be handled and processed in a context of strict quality control and auditing. From donor inclusion to FMT administration, measures should be taken to ensure high-quality standards and complete traceability. These measures

include the proper education of staff, the validation of laboratory procedures and equipment, and the recording of all essential information throughout all of the steps. Core data from the donation sample, results from sample testing and processing and the link to the recipient should be retained for 30 years to ensure traceability.[44] Ideally, the requirements for quality control should be ensured by regulation and inspection by the health authorities as elaborated below.

FECAL MICROBIOTA TRANSPLANTATION: A REGULATORY STRUGGLE

To assure a high level of safety and quality, the regulation of FMT and its related procedures by competent authorities is pivotal.

The regulation of FMT remains controversial and varies from nonexistent to very strict among countries. Since July 2016, in the United States, the US Food and Drug Administration (FDA) has regulated FMT as an investigational new drug (IND) with a legal exception applying to hospital physicians who treat patients with rCDI refractory to standard treatment.[57,58] To perform FMT for diseases other than rCDI, institutions are required to submit an IND application. This poses a marked limitation to the clinical and scientific application of FMT. The enforcement exception for FMT for rCDI form the sole regulatory framework for US FMT institutions to operate within. In Europe, the European Commission has taken the position that feces are uncontestably a tissue, but it does not naturally fall under the EUTCD.[59] Accordingly, the competent authorities have avoided common European definitions, leaving the regulation to be managed at a national enforcement level. Member states are free to create specific regulatory frameworks or apply existing regulatory frameworks, such as national requirements for tissue and cell transplantation.[59] Consequently, this leaves FMT largely unregulated in many European countries. In countries where specific legislation has been adopted, FMT is regulated as either a tissue or a drug.

The regulatory controversy revolves around whether feces are of nonhuman origin and therefore considered a drug or of human origin and therefore considered a tissue. The EUTCD committee recognizes that feces fulfill the criteria of being a tissue, but because the active substances in feces, that is, microbes and their products, are of nonhuman origin, they argue that feces cannot be covered by the EUTCD.[59] This view, however, may prove too narrow. The human microbiota has evolved over millions of years through coexistence with humans and is highly specific to the individual; therefore, it can easily be argued that the microbiota constitutes an integral part of the human body. In addition to microorganisms, epithelial cells shed from the gastrointestinal tract lining as well as immunoglobulins and metabolites are present in feces.[60] If and how these constituents contribute to the clinical effects of FMT is unknown, but it remains clear that they are also transferred during an FMT.[60]

Regulating FMT as a drug addresses the demand for safety, but the strict requirements for a reproducible product consistent in all its substances, which is inherent in drug legislation, is a requirement that donor microbiota cannot fulfill because of their individual and variable nature. The current drug legislation provides no legal basis to cover donor-related aspects or long-term traceability. The safety of FMT highly depends on the selection and screening of the donor because no standardization of the product exists and because pathogen reduction, such as that used for plasma-derived products, is inherently impossible for FMT products. Thus, for a single-donor procedure with unprocessed donor feces, drug legislation does not meet the key requirements for regulation.

Classifying FMT as a tissue would result in regulation allowing a variable product and would also cover the activities related to obtaining the product, as described above. This also applies at the organizational level, imposing requirements for donor selection, safe handling, documentation, and long-term traceability.

Depending on the organizational and financial structures of national health care systems, different countries may need to apply FMT regulations differently. Regulatory frameworks designed to fit, for example, the Scandinavian welfare model with public hospitals and free access to hospital services without charge to citizens would not work in countries with privately owned hospitals where patients pay out of pocket for hospital services. This renders the US IND model, which is necessary in a "for-profit" system, unfit in areas such as Scandinavia. To accommodate these differences, different approaches, such as those used for blood products, may be needed to sufficiently secure FMT for patients in different countries.

THE BLOOD SERVICE INFRASTRUCTURE AS A SUPERIOR PLATFORM

The requirements for an effective feces bank infrastructure parallel those of a blood service infrastructure. Blood service organizations handle donor recruitment and blood prescreening and screening, donation collection, processing, release, and storage. Adding stool collection to the blood service infrastructure may present a new opportunity for blood banks that already have well-established procedures, such as inspections on a regular basis from the health authorities.

Blood donors are a highly specific group of healthy people who have already volunteered to donate blood to help other human beings; therefore, they are more likely to volunteer and be eligible for feces donations. In a previous study, we found that 88% of blood donors who were asked to become feces donors were willing to do so.[47] Notably, we

also demonstrated that blood donors had an approximately 20% eligibility rate,[47] which was high compared with rates reported from other settings where feces donors were recruited outside of blood banks.[52] In general, most screened participants fail the screenings due to the age criteria, high body mass index, and allergies.[45,47,52] The main determinants of a high blood donor eligibility rate are their willingness to become feces donors, the absence of risk factors, and a low failure rate during the feces screening.[47] (For screening criteria, see Table S1). In practice, the recruitment process among blood donors ensures a scalable flow of healthy feces donors to meet the clinical demand for FMT.

With the blood bank infrastructure, FMT is scalable. Currently, FMT institutions operate within limits imposed by practical and economic barriers, and there is a strong economic argument (economies of scale and scope) for aligning FMT services with current blood bank organizations.

PERSPECTIVE

In this paper, we argue that existing blood services possess most of the infrastructure necessary to run and maintain a high-capacity FMT service. Currently, without appropriate legislation, FMT stands as a highly effective treatment caught in a regulatory dispute. Agreement on an applicable regulatory framework is imminent, but the continuous development of microbiota-based therapies makes it difficult for authorities to determine the most appropriate legislation. Regulation by competent authorities should mainly ensure a high degree of safety. At the same time, flexibility is required to ensure patient access to effective treatments, continuing innovation, and the investigation of new ideas. A European consensus that FMT is best regulated as a tissue transfer is emerging.[46,61,62] While tissue transfer regulation may apply to unprocessed, donor-specific, cryopreserved feces, the manipulation or standardization of feces into a well-defined substance makes the resulting product ideal for the drug legislation.[44] At the current stage, where we speculate that the combination of several different components ensures the high success rate of the treatment against CD infection, there is an urgent need to regulate the procedure under the tissue and cells legislation. If effective treatments based on well-defined and controlled preparations of bacteria, bacteriophages, bacterial metabolites, or immune system components become available, such treatments should be regulated under drug legislation. Currently, a clear regulatory definition of when tissue becomes a drug is crucial.

With an estimated 700,000 cases of CD infection annually in Europe and the United States,[63] FMT is an emerging therapy with the potential to become routine practice. Fulfilling a demand of this scale requires an extensive and robust infrastructure. Blood service organizations are suitable to perform the recruitment, prescreening, and screening of donors, as well as the processing and storage of the products. We have developed an effective FMT service through a fruitful collaboration between the blood service center and the department of hepatology and gastroenterology, assuring a high level of safety; therefore, we propose that FMT may represent a new frontier for blood banks.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

TABLE S1. Content of the fecal donor screening used to screen blood donors.